(FILE 'HOME' ENTERED AT 14:47:07 ON 29 JUN 1999)

FILE 'SCISEARCH, MEDLINE, CAPLUS, BIOSIS, CANCERLIT, INPADOC, JAPIO, MEDICONF, AGRICOLA, GENBANK' ENTERED AT 14:47:11 ON 29 JUN 1999

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L1          9946 S ECDYSONE
L2            65 S L1 AND HYDRAZINE
L3            53 DUP REM L2 (12 DUPLICATES REMOVED)
L4            53 SORT L3 PY
L5           173 S NONSTEROIDAL AND ECDYSONE AND AGONIST
L6            45 S L5 AND MIMIC
L7            31 DUP REM L6 (14 DUPLICATES REMOVED)
L8            31 SORT L7 PY
L9             0 S WING DK/AU
L10        12333 S WING ?/AU
L11       201449 S HIS
                E WING D?/AU
L12          361 S E3
L13            0 S L12 AND L1
L14           15 S L5 AND WING
L15           12 DUP REM L14 (3 DUPLICATES REMOVED)
L16           12 SORT L15 PY
L17           50 S L5 AND ?HYDRAZINE
L18           25 S L5 AND HYDRAZINE
L19           23 DUP REM L18 (2 DUPLICATES REMOVED)
L20           23 SORT L19 PY
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=> d Ti so au ab pi l201 1-23

L201 NOT FOUND
The L-number entered has not been defined in this session, or it has been deleted. To see the L-numbers currently defined in this session, enter DISPLAY HISTORY at an arrow prompt (=>).

=> d Ti so au ab pi l20 1-23

L20 ANSWER 1 OF 23 MEDLINE
TI RH 5849, a **nonsteroidal ecdysone agonist**: effects on a Drosophila cell line.
SO SCIENCE, (1988 Jul 22) 241 (4864) 467-9.
Journal code: UJ7. ISSN: 0036-8075.
AU Wing K D
AB The steroid molting hormone 20-hydroxyecdysone is the physiological inducer of molting and metamorphosis in insects. In **ecdysone** -sensitive Drosophila Kc cells, the insecticide RH 5849 (1,2-dibenzoyl-1-tert-butylhydrazine) mimics the action of 20-hydroxyecdysone by causing the formation of processes, an inhibition of cell proliferation, and induction of acetylcholinesterase. RH 5849 also competes with [3H]ponasterone A for high-affinity **ecdysone** receptor sites from Kc cell extracts. Resistant cell populations selected by growth in the continued presence of either RH 5849 or 20-hydroxyecdysone are insensitive to both compounds and exhibit a decreased titer of measurable **ecdysone** receptors. Although it is less potent than 20-hydroxyecdysone in both whole-cell and cell-free receptor assays, RH 5849 is the first **nonsteroidal ecdysone agonist**.

L20 ANSWER 2 OF 23 CAPLUS COPYRIGHT 1999 ACS
TI Other hormonal agents: **ecdysone agonists**
SO BCPC Monogr. (1989), 43(Prog. Prospects Insect Control), 107-18
CODEN: MBCCDO; ISSN: 0306-3941
AU Wing, K. D.; Ramsay, J. R.
AB A review with 34 refs. The novel insect growth regulator RH 5849 (1,2-dibenzoyl, 1-tert-Bu **hydrazine**), is the first **nonsteroidal ecdysone** mimic as detd. by data from Drosophila melanogaster and Plodia interpunctella tissue culture cells, **ecdysone** receptor exts. therefrom, and Manduca sexta larvae; this seems to be its primary mode of action in Lepidoptera. It also has chemosterilant activity on female Diptera, Coleoptera and Lepidoptera. RH 5849 thus represents a prototype ligand for a novel, invertebrate-specific target site.

L20 ANSWER 3 OF 23 CAPLUS COPYRIGHT 1999 ACS
TI The crystal structure of 1,2-dibenzoyl-1-tert-butylhydrazine, a

nonsteroidal ecdysone agonist, and its effects on spruce budworm (Choristoneura fumiferana)
SO Can. J. Chem. (1990) [redacted](7), 1178-81
CODEN: CJCHAG; ISSN: [redacted]8-4042
AU Chan, T. H.; Ali, A.; Britten, J. F.; Thomas, A. W.; Strunz, G. M.; Salonius, A.
AB The crystal structure of 1,2-dibenzoyl-1-tert-butylhydrazine (I), a **nonsteroidal ecdysone agonist**, has been established by direct methods. The N-N bond in I was found to adopt a gauche conformation with a dihedral angle of -71.8.degree. or -58.1.degree.. The two amide functions adopt different planar conformations. The compd. is found to have a potent effect on the development of spruce budworm (Choristoneura fumiferana) larvae, causing early apolysis and subsequent mortality at 0.2-10 ppm concn. in artificial diet.

L20 ANSWER 4 OF 23 MEDLINE
TI In vitro effect of **nonsteroidal ecdysone agonist** RH 5849 on fat body acid phosphatase activity in rice moth, Corcyra cephalonica (Insecta).
SO BIOCHEMISTRY INTERNATIONAL, (1991 May) 24 (1) 69-75.
Journal code: 9Y9. ISSN: 0158-5231.
AU Ashok M; Dutta-Gupta A
AB **Nonsteroidal ecdysone agonist** stimulates acid phosphatase activity in the fat body in vitro cultures obtained from ligated late-last instar larvae of Corcyra cephalonica. The **agonist** also stimulates general protein synthesis. This stimulation is both time as well as dose dependent (up to a dose of 1000 ng of the **agonist**). However, still higher concentrations (1500-4000 ng) tend to depress the degree of stimulation.

L20 ANSWER 5 OF 23 SCISEARCH COPYRIGHT 1999 ISI (R)
TI QUANTITATIVE STRUCTURE-ACTIVITY STUDIES OF INSECT GROWTH-REGULATORS .10. SUBSTITUENT EFFECTS ON LARVICIDAL ACTIVITY OF 1-TERT-BUTYL-1-(2-CHLOROBENZOYL)-2-(SUBSTITUTED BENZOYL)**HYDRAZINES** AGAINST CHILO-SUPPRESSALIS AND DESIGN SYNTHESIS OF POTENT DERIVATIVES
SO PESTICIDE BIOCHEMISTRY AND PHYSIOLOGY, (FEB 1994) Vol. 48, No. 2, pp. 135-144.
ISSN: 0048-3575.
AU OIKAWA N; NAKAGAWA Y; NISHIMURA K (Reprint); UENO T; FUJITA T
AB The larvicidal activity of 1-tert-butyl-1-(2-chlorobenzoyl)-2-(substituted benzoyl)**hydrazines** was measured against the rice stem borer (Chilo suppressalis) in the presence of piperonyl butoxide, an inhibitor of oxidative metabolism. Variations in the activity were quantitatively examined by use of physicochemical substituent parameters and regression analysis. The results indicated that the hydrophobicity of substituents is favorable in general but the bulkiness of substituents is unfavorable position-specifically. The most favorable substitution pattern is the para substitution with lower alkyls and halogens. Compounds in which substitution patterns are simultaneously optimized in two benzene rings in the molecule were designed and prepared according to the present and previous quantitative analyses. Some of them, including 1-tert-butyl-1-(3,5-dichloro- and 3,5-dimethylbenzoyl)-2-(4-ethylbenzoyl) **hydrazines** the second being RH-5992, were about 20-30 times as larvicidal as the unsubstituted compound, RH-5849, against the rice stem borer. (C) 1994 Academic Press,Inc.

L20 ANSWER 6 OF 23 MEDLINE
TI RH-5849, a **nonsteroidal ecdysone agonist**, does not mimic makisterone-A in Dysdercus koenigii.
SO EXPERIENTIA, (1994 May 15) 50 (5) 461-4.
Journal code: EQZ. ISSN: 0014-4754.
AU Koul O; Kapil R S
AB The response of final instar nymphs of Dysdercus koenigii to topical application of the non-steroidal **ecdysone agonist**, RH-5849, was dose dependent. The candidate compound produced mortality even at moderate doses, but precocious adult development was not observed. Similar results were obtained after oral administration or injection. Conversely, injections of makisterone-A (the principal moulting hormone of Dysdercus) into 5th instar nymphs resulted in precocious adult development within 4 days. We conclude that RH-5849 does not mimic makisterone-A, as is the case with **ecdysone**, and that toxicity is mediated instead through non-endocrine targets in this insect species.

L20 ANSWER 7 OF 23 SCISEARCH COPYRIGHT 1999 ISI (R)
TI MOLECULAR ANALYSIS OF THE MODE OF ACTION OF RH-5992, A LEPIDOPTERAN-SPECIFIC, **NONSTEROIDAL** ECDYSTEROID **AGONIST**
SO INSECT BIOCHEMISTRY AND MOLECULAR BIOLOGY, (JAN 1995) Vol. 25, No. 1, pp. 109-117.
ISSN: 0965-1748.
AU RETNAKARAN A (Reprint); HIRUMA K; PALLI S R; RIDDIFORD L M
AB The dibenzoyl **hydrazine**, RH-5992, induces precocious molting

in all lepidopteran larvae tested including the tobacco hornworm, Manduca sexta and the spruce budworm, Choristoneura fumiferana. Synthesis of a new cuticle including formation of a new head capsule that is incompletely sclerotized and lack of ecdysis are some of the major phenotypic effects. Similar to 20E, RH-5992 induces Manduca hormone receptor 3 (MHR3) mRNA and suppresses 14 kDa larval cuticular protein (LCP-14) transcript levels in 4th instar epidermis of Manduca, cultured in vitro. The ED(50) for induction of MHR3 was 1.4 x 10(-7) M, 10 times less than that of 20E, When the epidermis was exposed to 20E for 17 h and then cultured in hormone-free medium for a further 48 h, the LCP-14 mRNA level went up to nearly 60% of the maximal level reached in the untreated control, However, when RH-5992 was used, the level remained low even after 48 h, Dopa decarboxylase (DDC) transcription normally occurs at the end of the molt in preparation for sclerotization and in the epidermis cultured in vitro requires initial exposure to 20E for 17 h followed by its removal. Both in vivo and transient ill vitro treatment with RH-5992 prevented DDC expression for up to 48 h after the removal of the compound. Thus, RH-5992 mimics the action of 20E on the expression of these 3 genes, but its effects persist in the tissue much longer than 20E.

L20 ANSWER 8 OF 23 SCISEARCH COPYRIGHT 1999 ISI (R)
TI **NONSTEROIDAL** ECDYSTEROID **AGONISTS** - TOOLS FOR THE STUDY OF HORMONAL ACTION
SO ARCHIVES OF INSECT BIOCHEMISTRY AND PHYSIOLOGY, (1995) Vol. 28, No. 3, pp. 209-223.
ISSN: 0739-4462.
AU OBERLANDER H (Reprint); SILHACEK D L; PORCHERON P
AB The first non-steroidal ecdysteroid **agonists** are dibenzoyl **hydrazines** and are typified by the compounds designated RH-5849 and RH-5992. The discovery that these compounds mimic 20E in a variety of insect orders, and especially the Lepidoptera, generated great interest from the research and agricultural communities. Such compounds provide important new research tools for physiological, biochemical, and molecular studies. In addition, the potential for application to agricultural pests looks very promising, especially for RH-5992 (tebufenozide). This review evaluates the evidence on the specificity of the ecdysteroid-like actions of these materials and considers their application for research and pest management. (C) 1995 Wiley-Liss, Inc.

L20 ANSWER 9 OF 23 MEDLINE
TI Cloning and developmental expression of the **ecdysone** receptor gene from the spruce budworm, Choristoneura fumiferana.
SO DEVELOPMENTAL GENETICS, (1995) 17 (4) 319-30.
Journal code: DEG. ISSN: 0192-253X.
AU Kothapalli R; Palli S R; Ladd T R; Sohi S S; Cress D; Dhadialla T S; Tzertzinis G; Retnakaran A
AB Degenerate oligonucleotides were designed on the basis of conserved amino acid sequences in the DNA and ligand-binding regions of the members of the steroid hormone receptor superfamily. Using these oligonucleotides in RNA-PCR, a cDNA fragment was isolated from the spruce budworm, Choristoneura fumiferana. Comparison of the deduced amino acid sequence of this cDNA fragment with the members of the steroid hormone receptor superfamily suggested that this PCR fragment is a region of the **ecdysone** receptor from C. fumiferana. Using this cDNA fragment as a probe, 10 clones were isolated from a cDNA library that was constructed using the RNA from 4- and 5-day old embryos of C. fumiferana. Two cDNA clones (1.3 and 3 kb) that overlap and show amino acid identity with Drosophila melanogaster **ecdysone** receptor B-1 isoform (DmEcR) were characterized and sequenced. The longest open reading frame had 539 codons and covered the complete EcR coding region. The deduced amino acid sequence of this open reading frame had all five of the regions typical for a steroid hormone nuclear receptor. The C domain or DNA binding region showed the highest identity wit EcR proteins from D. melanogaster, Chironomus tendons, Aedes aegypti, Manduca sexta, and Bombyx mori. The A/B region, D domain or hinge region, E domain, or ligand binding region also showed significant amino acid similarity with the EcR proteins from the five insects mentioned above. The C. fumiferana ecdysteroid receptor (CfEcR) cDNA probe detected a 6.0-kb mRNA that was present throughout the development of C. fumiferana. The CfEcR mRNA increases in abundance at the time of the ecdysteroid peak during the molting phase in the embryonic, larval and pupal stages but remains low during the intermolt period. In the 6th instar larvae, the 6-kb CfEcR mRNA was detected in the epidermis, fat body, and midgut and maximum expression was observed during the prepupal peak of ecdysteroids in the hemolymph. CfEcR mRNA was induced in **ecdysone** treated CF-203 cells as well in the epidermis and midgut of larvae that were fed the **nonsteroidal** ecdysteroid **agonist**, RH-5992. The induction occurred within an hour and reached maximum levels around 3 hr, after which it decreased to the basal level by 6 hr. In vitro transcription and translation of the CfEcR cDNA yielded a 67-Kda protein that bound to the **ecdysone** response element (EcRE) as a heterodimer, along with the ultraspiracle protein.

L20 ANSWER 10 OF 23 CAPLUS COPYRIGHT 1999 ACS
TI Anthelmintic N-alkyl-N'-diacylhydrazines: **nonsteroidal ecdysone agonists**
SO U.S., 87 pp. Cont. of U.S. Ser.No. 208,339, abandoned.
CODEN: USXXAM
IN Wing, Keith D.
AB This invention relates to methods of controlling helminths by contacting the helminths with a compd. having a nucleus of the formula A'C(:X)NR2NR1C(:X')B' wherein X and X' are the same or different O, S, or NR and A', B', R1 and R2 are a variety of substituents. Thus, e.g., reaction of t-butylhydrazine hydrochloride with benzoyl chloride afforded N'-t-butyl-N,N'-dibenzoylhydrazine (I) which induced the onset of molting in M. sexta L5D0 whole larvae: ED50 = 3.0 ppm (in diet) and 3.4 .mu.g/g body wt. (injected) vs. >2000 ppm and 181.0 .mu.g/g, resp., for 20-hydroxyecdysone. Although I displayed 30-fold lower binding affinity to the **ecdysone** receptor than 20-hydroxyecdysone, I is more potent at eliciting whole animal effects. There is an excellent correlation between the southern armyworm activity of 373 analogs of I and **ecdysone** receptor binding (R = 0.79). In hornworm larvae, I, an **ecdysone agonist**, exerts neg. feedback inhibition on hormone biosynthesis.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 5424333	A	19950613	US 91-725925	19910705
US 4985461	A	19910115	US 85-789797	19851021
AT 60979	E	19910315	AT 86-308068	19861017
ZA 8607921	A	19870624	ZA 86-7921	19861020
BR 8605121	A	19870721	BR 86-5121	19861020
US 5354762	A	19941011	US 87-12380	19870219
ZA 8701432	A	19871028	ZA 87-1432	19870227
US 5225443	A	19930706	US 91-501142	19910624

L20 ANSWER 11 OF 23 AGRICOLA
TI Forest insect cell lines responsive to 20-hydroxyecdysone and two **nonsteroidal ecdysone agonists**, RH-5849 and RH-5992.
SO Journal of insect physiology, June 1995. Vol. 41, No. 6. p. 457-464
Publisher: Exeter : Elsevier Science Ltd.
CODEN: JIPHAF; ISSN: 0022-1910
AU Sohi, S.S.; Palli, S.R.; Cook, B.J.; Retnakaran, A.
AB The effects of 20-hydroxyecdysone (20E) and two substituted dibenzoylbutylhydrazines, RH-5849 and RH-5992, were investigated in vitro using three forest insect cell lines. Two of these cell lines, IPRI-MD-66 (MD-66) from the forest tent caterpillar, Malacosoma disstria and IPRI-CF-1 (CF-1) from the spruce budworm, Choristoneura fumiferana, grow freely suspended, whereas the cells of the third line, FPMI-CF-70 (CF-70) from C. fumiferana, stay attached to the culture flask. MD-66 cells responded to all three by forming clumps and by producing filamentous extensions. In addition, these compounds produced increased cell attachment and reduced cell proliferation in this cell line. CF-70 cells also responded to all three compounds although to a lesser extent. On the other hand, CF-1 cells showed little or no morphological response. The above effects of RH-5992 on MD-66 cells were both dose and time dependent. This compound also induced the expression of thee Malacosoma disstria hormone receptor (MdHR3) in these cells in a dose dependent manner, as was the case with 20E. This result indicated that effect of RH-5992 on MD-66 cells is specific and related to their response to 20E. These phenotypic and molecular observations indicate that MD-66 cells and RH-5992 will be an excellent in vitro model system for studying the mode of action of ecdysteroid **agonists**.

L20 ANSWER 12 OF 23 SCISEARCH COPYRIGHT 1999 ISI (R)
TI ECDYSTEROID RECEPTOR-BINDING ACTIVITY AND ECDYSTEROID **AGONIST** ACTIVITY AT THE LEVEL OF GENE-EXPRESSION ARE CORRELATED WITH THE ACTIVITY OF DIBENZOYL **HYDRAZINES** IN LARVAE OF BOMBYX-MORI
SO JOURNAL OF INSECT PHYSIOLOGY, (OCT 1996) Vol. 42, No. 10, pp. 937-941.
ISSN: 0022-1910.
AU MIKITANI K (Reprint)
AB Ecdysteroid activities of two dibenzoyl **hydrazines** (RH 5849 and RH 5992) were examined using the Kc cell line. Gene expression activity was determined in the transient assay utilizing the ecdysteroid responsive Drosophila melanogaster hsp27 promoter gene. Ecdysteroid receptor binding (EC(50) = 3.0 x 10(-7) M), induction of ecdysteroid responsive gene expression (EC,, = 3.0 x 10(-6) M) and induction of cell morphological change (EC(50) = 3.0 x 10(-7) M) were 13-fold, 7-fold and 13-fold higher in RH 5992 than in RH 5849, respectively. The addition of 10 ppm RH 5849 to the diet induced head capsule slippage in Bombyx mori larvae and most of the larvae died, RH 5992 caused the same response at 1 ppm. The higher insecticidal activity of RH 5992 compared to RH 5849 is likely caused by its higher ecdysteroid **agonist** activity at the molecular level. Copyright (C) 1996 Elsevier Science Ltd

L20 ANSWER 13 OF 23 SCISEARCH COPYRIGHT 1999 ISI (R)
TI THEORETICAL-STUDY OF THE STRUCTURE AND ROTATIONAL FLEXIBILITY OF DIACYLHYDRAZINES - IMPLICATIONS FOR THE STRUCTURE OF **NONSTEROIDAL ECDYSONE AGONISTS** AND AZAPEPTIDES
SO JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, (02 OCT 1996) Vol. 118, No. 39, pp. 9395-9401.
ISSN: 0002-7863.
AU REYNOLDS C H (Reprint); HORMANN R E
AB High-level ab initio calculations have been used to determine the minimum energy structures of N,N'-diformylhydrazine, N-methyl-N,N'-diformylhydrazine, and N,N'-dimethyl-N,N'-diformylhydrazine. These calculations show that the global minimum is a nonplanar structure in which the nitrogen lone pairs are essentially perpendicular to one another. However, the energy required for (Z,Z)-diformylhydrazine to adopt a planar structure is less than 1 kcal/mol (MP2/6-31+G**). This is due to attractive intramolecular hydrogen bonds between the N-hydrogens and the carbonyl oxygens in the planar geometry. When one or both amide configurations are inverted (Z,E; E,E), or when the nitrogens are substituted, with methyl for example, these hydrogen bonds are lost and the planar structure becomes much less stable relative to the twisted rotamer. Thus, we conclude from these calculations that diacylhydrazines are intrinsically nonplanar with respect to the CO-N-N-CO torsion, and that with the exception of (Z,Z)-diformylhydrazine the rotational barriers are large. The observation of a planar crystal structure for diformylhydrazine is due to additional intermolecular hydrogen bonds which are available to planar diformylhydrazine in the crystal lattice. Finally, these calculations have significant implications for the structure and dynamical properties of **nonsteroidal ecdysone agonists**, azapeptides, and azatides which incorporate the diacylhydrazine structure.

L20 ANSWER 14 OF 23 SCISEARCH COPYRIGHT 1999 ISI (R)
TI Structure-activity study and conformational analysis of RH-5992, the first commercialized **nonsteroidal ecdysone agonist**
SO ACS SYMPOSIUM SERIES, (MAR 1997) Vol. 658, pp. 206-219.
Publisher: AMER CHEMICAL SOC, 1155 SIXTEENTH ST NW, WASHINGTON, DC 20036.
ISSN: 0097-6156.
AU Hsu A C T (Reprint); Fujimoto T T; Dhadialla T S
AB In the early 1980's, the first compound from a class of 1,2-diacyl-1-substituted **hydrazines** was synthesized and discovered to have insecticidal activity. RH-5849, which was synthesized subsequently in the analog synthesis program, demonstrated lethal and unusual effects on the development of Lepidopteran insects. A thorough made of action study further demonstrated that RH-5849 was the first non-steroidal **ecdysone agonist**. These early results triggered a tremendous amount of laboratory and field research around the world, in order to understand the full impact of this new class of environmentally friendly insecticides. This paper will discuss: (a) the structure activity study that led to the discovery and eventually the commercialization of RH-5992, bearing the trade name: CONFIRM(R) (in USA) and MIMIC(RM) (outside USA), (b) summary of the mode of action of RH-5992 as an **ecdysone agonist**, and (c) conformational analysis of RH-5992.

L20 ANSWER 15 OF 23 SCISEARCH COPYRIGHT 1999 ISI (R)
TI Ultrastructural effects of a non-steroidal **ecdysone agonist**, RH-5992, on the sixth instar larva of the spruce budworm, Choristoneura fumiferana
SO JOURNAL OF INSECT PHYSIOLOGY, (JAN 1997) Vol. 43, No. 1, pp. 55-68.
Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD, ENGLAND OX5 1GB.
ISSN: 0022-1910.
AU Retnakaran A (Reprint); MacDonald A; Tomkins W L; Davis C N; Brownwright A J; Palli S R
AB Force feeding of RH-5992 (Tebufenozide), a non-steroidal **ecdysone agonist** to newly moulted sixth instar larvae of the spruce budworm, Choristoneura fumiferana, (Lepidoptera: Tortricidae) initiates a precocious, incomplete moult, Within 6 h post treatment (pt) the larva stops feeding and remains quiescent, Around 12 h pt, the head capsule slips partially revealing an untanned new head capsule that appears wrinkled and poorly formed, By 24 h pt, the head capsule slippage is pronounced and there is a mid-dorsal split of the old cuticle in the thoracic region but there is no ecdysis, The larva remains moribund in this state and ultimately dies of starvation and desiccation. The temporal sequence of the external and internal changes of the integument were studied using both scanning and transmission electron microscopy. Within 3 h pt, there is hypertrophy of the Golgi complex indicating synthetic activity and soon after, large, putative ecdysial droplets are seen, Within 24 h, a new cuticle that lacks the endocuticular lamellae is formed, The formation of the various cuticular components, the degradation of the old cuticle and changes in the organelles of the epidermal cells of the mesothoracic tergite are described, The difference between the natural

moult and the one induced by RH-5992 are explained on the basis of molecular events that take place during the moulting cycle, The persistence of this **ysone agonist** in the tissues permits the expressi of all the genes that are up-regulated the presence of the natural hormone but those that are turned on in the absence of the hormone are not expressed. (C) 1997 Elsevier Science Ltd.

L20 ANSWER 16 OF 23 SCISEARCH COPYRIGHT 1999 ISI (R)
TI The ecdysoid RH5849 induces yolk polypeptide synthesis in male flies
SO INVERTEBRATE REPRODUCTION & DEVELOPMENT, (JAN 1997) Vol. 31, No. 1-3, pp. 69-74.
Publisher: INT SCIENCE SERVICES/BALABAN PUBLISHERS, PO BOX 2039, REHOVOT, ISRAEL.
ISSN: 0168-8170.
AU deLoof A (Reprint); Wei Z; Huybrechts R; Gijbels J; Verhaert P
AB RH5849 is a benzoyl **hydrazine** analog which has been reported to mimic several effects of the arthropod steroid hormone **ecdysone** to which it is chemically totally unrelated. In adult Diptera, **ecdysone** is the hormone that triggers vitellogenin synthesis. We report here that RH5849, upon oral ingestion, is able to induce vitellogenin synthesis in male Drosophila, Neobellieria, Phormia and Lucilia. This contrasts to data in the literature which showed that RH5849 could not mimic the pupariation-inducing effect of **ecdysone** in last instar fly larvae. RH5849 neither exerts a juvenile hormone mimicking effect nor behaves as an anti-juvenile hormone in both the Colorado potato beetle and Galleria.

L20 ANSWER 17 OF 23 MEDLINE
TI Molting hormonal and larvicidal activities of aliphatic acyl analogs of dibenzoylhydrazine insecticides.
SO STEROIDS, (1997 Oct) 62 (10) 638-42.
Journal code: V10. ISSN: 0039-128X.
AU Shimizu B; Nakagawa Y; Hattori K; Nishimura K; Kurihara N; Ueno T
AB Dibenzoylhydrazines are the **nonsteroidal ecdysone agonists**. Using comparative molecular field analysis, we previously found that the alkyl side chain of 20-hydroxyecdysone (20E) is three-dimensionally superposable with one of their two aryl moieties. To identify the aryl moiety that is better superposable on the alkyl chain, we synthesized compounds in which one of the two aryl groups of tebufenozide (N-t-butyl-N-3,5-dimethylbenzoyl-N'-4-ethylbenzoylhydrazine) is replaced by alkyl groups such as C4H9, C5H11, and C6H13. The molting hormonal activity of these compounds was measured using cultured integuments prepared from rice stem borers, Chilo suppressalis Walker, in terms of stimulation of incorporation of N-acetyl-[14C]glucosamine. N-t-Butyl-N-3,5-dimethylbenzoyl-N'-acylhydrazines with a hexanoyl or heptanoyl group were about 20-fold higher than that of 20E, whereas N-acyl-N-t-butyl-N'-4-ethylbenzoylhydrazines with a hexanoyl or heptanoyl group were much weaker than 20E. Their larvicidal activity was also measured against rice stem borers. The former series of compounds were much more active than the other series as well as 20E. Thus, the benzoyl moiety of dibenzoylhydrazines, which is bound to the secondary nitrogen atom (-NH-), is replaceable by aliphatic acyl groups without greatly affecting the biological activities.

L20 ANSWER 18 OF 23 MEDLINE
TI Induction of enzymes involved in molting hormone (ecdysteroid) inactivation by ecdysteroids and an **agonist**, 1,2-dibenzoyl-1-tert-butylhydrazine (RH-5849).
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Mar 28) 272 (13) 8427-32.
Journal code: HIV. ISSN: 0021-9258.
AU Williams D R; Chen J H; Fisher M J; Rees H H
AB Molting in insects is regulated by molting hormones (ecdysteroids). The major active hormone, 20-hydroxyecdysone, is formed by **ecdysone** 20-monooxygenase-catalyzed hydroxylation of **ecdysone**. During times of decreasing hormone titers, inactivation occurs by several routes including (i) 26-hydroxylation and further oxidation to the 26-oic acid, (ii) formation of various conjugates (e.g. phosphates), and (iii) in Lepidoptera in particular, **ecdysone** oxidase-catalyzed formation of 3-dehydroecdysteroid, which is reduced to 3-epiecdysteroid, followed by phosphotransferase-catalyzed formation of phosphate conjugates. Administration of the **nonsteroidal** ecdysteroid **agonist** RH-5849 (1,2-dibenzoyl-1-tert-butylhydrazine), but not 20-hydroxyecdysone, to tobacco hornworm (Manduca sexta) resulted in induction of midgut cytosolic **ecdysone** oxidase and ecdysteroid phosphotransferase activities. In addition, both 20-hydroxyecdysone and RH-5849 caused induction of ecdysteroid 26-hydroxylase activity in midgut mitochondria and microsomes, whereas 20-hydroxylase was induced to a lesser extent by 20-hydroxyecdysone in mitochondria and by either RH-5849 or 20-hydroxyecdysone in microsomes. Commensurate with induction of the enzymes by ecdysteroid and RH-5849 is a requirement for RNA and protein synthesis, without precluding indirect mechanisms. These results indicate that molting hormone stimulates at least one universal route of its own

inactivation by inducing ecdysteroid 26-hydroxylase activity and are discussed in relation to an analogous phenomenon observed for vitamin D inactivation in vertebrates.

L20 ANSWER 19 OF 23 AGRICOLA
TI Effects of ecdysteroid **agonist** RH-5849 on pupal diapause of the tobacco hornworm (Manduca sexta).
SO Archives of insect biochemistry and physiology, 1997. Vol. 35, No. 1/2. p. 191-197
Publisher: New York, N.Y. : Wiley-Liss.
CODEN: AIBPEA; ISSN: 0739-4462
AU Sielezniew, M.; Cymborowski, B.
AB The tobacco hornworm (Manduca sexta) exhibits facultative pupal diapause which is induced by the exposure of young larval instars to short day lengths. The daily body weight of pupae kept in constant humidity and the absence of eye pigmentation, were used as good markers for diapause in this species. The **nonsteroidal ecdysone agonist**, RH-5849, has proven to be very effective in inducing adult development in diapausing pupae in a dose-dependent manner. It was found that injection of 0.5 micrograms/g of pupal weight of acetone solution of this compound resulted in immediate cessation of the diapause and led to normal adult development and emergence. Higher doses (1-2 micrograms/g of body weight) caused emergence of the adults having deformed wings. Doses exceeding 2.5 micrograms/g of pupal weight caused hyperecdysonism, resulting in abnormal premature development without emerging from pupae. RH-5849 dissolved in acetone is about 13 times more effective in breaking the diapause as compared with the ethanol solution.

L20 ANSWER 20 OF 23 AGRICOLA
TI Effects of the non-steroidal ecdysteroid mimic tebufenozide on the tomato looper Chrysodeixis chalcites (Lepidoptera: Noctuidae): an ultrastructural analysis.
SO Archives of insect biochemistry and physiology, 1997. Vol. 35, No. 1/2. p. 179-190
Publisher: New York, N.Y. : Wiley-Liss.
CODEN: AIBPEA; ISSN: 0739-4462
AU Smagghe, G.; Vinuela, E.; Budia, F.; Degheele, D.
AB Oral treatment indicated that the substituted dibenzoylhydrazine tebufenozide is a potent **nonsteroidal agonist** of ecdysteroids when tested on last instar larvae of the tomato looper Chrysodeixis chalcites. Treated larvae showed characteristic signs of precocious moulting within 12 h of treatment, leading to head capsule apolysis and cessation of feeding. Electron microscopic analysis of treated integument revealed a forced, untimely synthesis of a new (epi)cuticle via epidermal cell activation; however, normal procuticle secretion was interrupted since the large number of procuticular lamellae that normally appear in controls was conspicuously absent. Further, phenotypic changes of endocrine gland ultrastructure and that of the foregut epithelium and muscle organization were also observed. This compound appears to be a useful tool in endocrine research and in the control of lepidopteran pests.

L20 ANSWER 21 OF 23 SCISEARCH COPYRIGHT 1999 ISI (R)
TI Interactions of ecdysteroid and juvenoid **agonists** in Plodia interpunctella (Hubner)
SO ARCHIVES OF INSECT BIOCHEMISTRY AND PHYSIOLOGY, (10 JUN 1998) Vol. 38, No. 2, pp. 91-99.
Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012.
ISSN: 0739-4462.
AU Oberlander H (Reprint); Silhacek D L; Leach C E
AB The influence of non-steroidal ecdysteroid **agonists** on Indian-meal moth larvae was assessed by rearing last instar larvae on diet treated with RH-5992 (tebufenozide) or RH-2485 (methoxyfenozide). Larvae were monitored for effects of the ecdysteroid **agonists** on weight, metamorphosis and mortality. Larvae treated with either of the ecdysteroid **agonists** at a concentration of 5 ppm or higher gained less weight and had greater mortality than did larvae reared on control diet. For example, the weights of control larvae increased approximately 400% by day 2, compared with only a 50% increase in weight when the larvae were treated with 25 ppm of RH-2485 or RH-5992. Similarly, mortality in control larvae was less than 10%, but was as much as 90-100% in larvae reared on diet treated with one of the ecdysteroid **agonists**. We also examined the effects of simultaneous treatment with a juvenile hormone (JH) mimic, either methoprene or fenoxycarb. The JH mimics prevented adult emergence, and the larvae continued to feed throughout the month-long observation period. However, larvae treated with a juvenile hormone mimic gained weight despite the presence of an ecdysteroid **agonist** in the diet. On diets treated with 0.1 ppm of RH-2485 or RH-5992, JH-treated larvae gained even more weight than did untreated controls. Interestingly, although the addition of a JH mimic to ecdysteroid-treated diet resulted in increased weight, it did not lead to

reduced mortality. In fact, combinations of a JH mimic with 10 ppm RH 2485 or RH 5992 resulted in nearly 100% mortality compared with 40-70% mortality without the JH compounds. These results indicate that JH mimics overcome the inhibitory effects of ecdysteroid **agonists** on weight gain; however, they also resulted in increased mortality compared with moderate doses of ecdysteroid **agonists** alone. One specific action of these compounds at the cellular level was noted in that RH 5992 mimicked ecdysteroids by increasing uptake of C-14-GlcNAc in a Plodia interpunctella cell Line, while fenoxycarb was inhibitory. (C) 1998 Wiley-Liss, Inc.dagger.

L20 ANSWER 22 OF 23 MEDLINE
TI Ecdysteroid resistant subclones of the epithelial cell line from Chironomus tentans (Insecta, Diptera). I. Selection and characterization of resistant clones.
SO IN VITRO CELLULAR AND DEVELOPMENTAL BIOLOGY. ANIMAL, (1998 Feb) 34 (2) 116-22.
Journal code: BZE. ISSN: 1071-2690.
AU Spindler-Barth M; Spindler K D
AB Chironomus tentans cells were cultured in the presence of gradually increasing concentrations of 20-OH-**ecdysone** or a **nonsteroidal** molting hormone **agonist**, the benzoylhydrazine RH 5992, for a period of about 2 yr. From these cultures, subclones were selected, which are resistant to up to 25 microM 20-OH-**ecdysone** according to morphological (changes in cell shape and cell arrangement) and physiological criteria (acetylcholinesterase induction, secretion of chitinolytic enzymes, thymidine incorporation). Some subclones, selected in the presence of 20-OH-**ecdysone**, are resistant only to molting hormone, but still respond to RH 5992 morphologically and biochemically, whereas subclones selected in the presence of the benzoylhydrazine showed no reaction neither to 20-OH-**ecdysone** nor to the hormone **agonist**. Hormone resistance is stable; 3 mo. after hormone withdrawal, resistant clones still do not respond to renewed exposure to 20-OH-**ecdysone** or RH 5992, respectively. Because in all resistant subclones tested so far all hormonally regulated responses known from sensitive cells were no longer detectable, it is assumed that the hormone signaling pathway itself is interrupted. Possible mechanisms of hormone resistance were discussed.

L20 ANSWER 23 OF 23 SCISEARCH COPYRIGHT 1999 ISI (R)
TI Comparative ecdysteroid action of ring-substituted dibenzoylhydrazines in Spodoptera exigua
SO ARCHIVES OF INSECT BIOCHEMISTRY AND PHYSIOLOGY, (MAR 1999) Vol. 41, No. 1, pp. 42-53.
Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012.
ISSN: 0739-4462.
AU Smagghe G (Reprint); Nakagawa Y; Carton B; Mourad A K; Fujita T; Tirry L
AB Ring-substituted dibenzoylhydrazines are well known as **nonsteroidal ecdysone agonists** that cause precocious larval molt leading to death. Among them, tebufenozide (RH-5992) is used in practice as insecticide to control lepidopteran pests selectively. Recently, a new dibenzoylhydrazine, methoxyfenozide (RH-2485), with a higher activity for Lepidoptera, has been discovered. To obtain insight into the molecular mechanisms involved in the insecticidal selectivity of the dibenzoylhydrazine family, we measured the in vivo toxicity of these dibenzoyl **hydrazines** against larval stages of the beet armyworm, Spodoptera exigua, and their action on in vitro cultured imaginal discs. We found that both **nonsteroidal ecdysone agonists** induced premature and lethal molting, and caused the same effect as 20-hydroxyecdysone in vitro. Furthermore, we measured the larvicidal activity against S. exigua of a series of dibenzoylhydrazines, in which ring-substituents were varied in a range of halogen, lower alkyl, OCH3, SCH3, Ph, CN, NO2, and CF3. The substituent effects on the larvicidal activity against S. exigua were very similar to that for another lepidopteran insect species Chilo suppressalis, suggesting that the molecular mechanism of action of these compounds is similar within both lepidopteran species. Arch. Insect Biochem. Physiol. 41:42-53, 1999. (C) 1999 Wiley-Liss, Inc.

(FILE 'HOME' ENTERED AT 14:47:07 ON 29 JUN 1999)

FILE 'SCISEARCH, MEDLINE, CAPLUS, BIOSIS, CANCERLIT, INPADOC, JAPIO, MEDICONF, AGRICOLA, GENBANK' ENTERED AT 14:47:11 ON 29 JUN 1999

L1	9946	S ECDYSONE
L2	65	S L1 AND HYDRAZINE
L3	53	DUP REM L2 (12 DUPLICATES REMOVED)
L4	53	SORT L3 PY
L5	173	S NONSTEROIDAL AND ECDYSONE AND AGONIST
L6	45	S L5 AND MIMIC
L7	31	DUP REM L6 (14 DUPLICATES REMOVED)
L8	31	SORT L7 PY
L9	0	S WING DK/AU
L10	12333	S WING ?/AU
L11	201449	S HIS
		E WING D?/AU
L12	361	S E3
L13	0	S L12 AND L1
L14	15	S L5 AND WING
L15	12	DUP REM L14 (3 DUPLICATES REMOVED)
L16	12	SORT L15 PY
L17	50	S L5 AND ?HYDRAZINE
L18	25	S L5 AND HYDRAZINE
L19	23	DUP REM L18 (2 DUPLICATES REMOVED)
L20	23	SORT L19 PY
L21	0	S L1 AND DIBENZOYLALKYL
L22	1	S L1 AND ISOBUTYL-BENZAMIDE
L23	0	S L1 AND CYANOHYDRAZINE
L24	0	S L1 AND CYANO-HYDRAZINE
L25	1	S L1 AND ACETYLHARPAGIDE
L26	1	S L1 AND (DIACYL HYDRAZINE)

L25 ANSWER 1 OF 1 SCISEARCH COPYRIGHT 1999 ISI (R)
TI 8-O-**acetylharpagide** is a nonsteroidal ecdysteroid agonist
SO INSECT BIOCHEMISTRY AND MOLECULAR BIOLOGY, (JUN 1996) Vol. 26, No. 6, pp. 519-523.
Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD, ENGLAND OX5 1GB.
ISSN: 0965-1748.
AU Elbrecht A (Reprint); Chen Y L; Jurgens T; Hensens O D; Zink D L; Beck H T; Balick M J; Borris R
AB We have identified a novel nonsteroidal ecdysteroid agonist, This compound was isolated from a methanol extract of Ajuga reptans L. (Lamiaceae) and the structure was identified by spectroscopic methods as 8-O-**acetylharpagide**. We have characterised this compound as an ecdysteroid agonist in a transactivation assay using beta-galactosidase as the reporter gene regulated by ecdysteroid response elements. In this assay, 8-O-**acetylharpagide** has an EC(50) of 22 mu M. The compound also competes with tritiated-ponasterone A for binding to the Drosophila ecdysteroid receptor, Finally, it induces differentiation of Drosophila Kc cells as would be expected of an ecdysteroid agonist, This iridoid glycoside is common to several plant species and may play a role in the natural defense mechanisms of plants. Copyright (C) 1996 Elsevier

L26 ANSWER 1 OF 1 CAPLUS COPYRIGHT 1999 ACS

TI A nuclear receptor from Bombyx that act as a transcriptional regulator and its use in the expression of transgenes in animal cells

SO PCT Int. Appl., 143 pp.
CODEN: PIXXD2

IN Gage, Fred H.; Suhr, Steven T.

AB A nuclear receptor (bR) of the silk moth Bombyx mori that is useful for the regulation of expression of foreign genes in insect cells is described. BR is thought to be a strong transcriptional regulator in cells of B. mori and it is found to be functional in mammalian cells. Addn. of activation domains to the bR open-reading frame increases the activity of the ligand modulated regulator to afford high-level transcriptional induction. Further modifications to the bR ligand binding domain result in receptors with unique transactivational characteristics. A major advantage of the use of bR is that its natural ligand is not manufd. by mammalian cells, such as **diacyl hydrazines**, allowing strict control of gene expression using relatively small proteins. A particular example of this is a fusion protein of the receptor, the activation domain of VP16 and the tet repressor called TTMT (Tebufenozide/Tetracycline Modulated Transactivator) that uses the tetO operator and the **ecdysone** response element to regulate gene expression by repression (with tetracyclines) and activation by acylhydrazines. Regulation of expression of a reporter gene from a TTMT-responsive promoter by tebufenozide and muristerone A is demonstrated.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9902683	A1	19990121	WO 98-US14215	19980710
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9883895	A1	19990208	AU 98-83895	19980710

L4 ANSWER 23 OF 53 CAPLUS COPYRIGHT 1999 ACS

TI Anthelmintic N-alkyl-N,N'-diacylhydrazines: nonsteroidal **ecdysone** agonists

SO U.S., 87 pp. Cont. of U.S. Ser.No. 208,339, abandoned.
CODEN: USXXAM

IN Wing, Keith D.

AB This invention relates to methods of controlling helminths by contacting the helminths with a compd. having a nucleus of the formula A'C(:X)NR2NR1C(:X')B' wherein X and X' are the same or different O, S, or NR and A', B', R1 and R2 are a variety of substituents. Thus, e.g., reaction of t-butylhydrazine hydrochloride with benzoyl chloride afforded N'-t-butyl-N,N'-dibenzoylhydrazine (I) which induced the onset of molting in M. sexta L5D0 whole larvae: ED50 = 3.0 ppm (in diet) and 3.4 .mu.g/g body wt. (injected) vs. >2000 ppm and 181.0 .mu.g/g, resp., for 20-hydroxyecdysone. Although I displayed 30-fold lower binding affinity to the **ecdysone** receptor than 20-hydroxyecdysone, I is more potent at eliciting whole animal effects. There is an excellent correlation between the southern armyworm activity of 373 analogs of I and **ecdysone** receptor binding (R = 0.79). In hornworm larvae, I, an **ecdysone** agonist, exerts neg. feedback inhibition on hormone biosynthesis.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5424333	A	19950613	US 91-725925	19910705
	US 4985461	A	19910115	US 85-789797	19851021
	AT 60979	E	19910315	AT 86-308068	19861017
	ZA 8607921	A	19870624	ZA 86-7921	19861020
	BR 8605121	A	19870721	BR 86-5121	19861020
	US 5354762	A	19941011	US 87-12380	19870219
	ZA 8701432	A	19871028	ZA 87-1432	19870227

L20 ANSWER 18 OF 23 MEDLINE
TI Induction of enzymes involved in molting hormone (ecdysteroid) inactivation by ecdysteroids and an **agonist**, 1,2-dibenzoyl-1-tert-butylhydrazine (RH-5849).
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Mar 28) 272 (13) 8427-32. Journal code: HIV. ISSN: 0021-9258.
AU Williams D R; Chen J H; Fisher M J; Rees H H
AB Molting in insects is regulated by molting hormones (ecdysteroids). The major active hormone, 20-hydroxyecdysone, is formed by **ecdysone** 20-monooxygenase-catalyzed hydroxylation of **ecdysone**. During times of decreasing hormone titers, inactivation occurs by several routes including (i) 26-hydroxylation and further oxidation to the 26-oic acid, (ii) formation of various conjugates (e.g. phosphates), and (iii) in Lepidoptera in particular, **ecdysone** oxidase-catalyzed formation of 3-dehydroecdysteroid, which is reduced to 3-epiecdysteroid, followed by phosphotransferase-catalyzed formation of phosphate conjugates. Administration of the **nonsteroidal** ecdysteroid **agonist** RH-5849 (1,2-dibenzoyl-1-tert-butylhydrazine), but not 20-hydroxyecdysone, to tobacco hornworm (Manduca sexta) resulted in induction of midgut cytosolic **ecdysone** oxidase and ecdysteroid phosphotransferase activities. In addition, both 20-hydroxyecdysone and RH-5849 caused induction of ecdysteroid 26-hydroxylase activity in midgut mitochondria and microsomes, whereas 20-hydroxylase was induced to a lesser extent by 20-hydroxyecdysone in mitochondria and by either RH-5849 or 20-hydroxyecdysone in microsomes. Commensurate with induction of the enzymes by ecdysteroid and RH-5849 is a requirement for RNA and protein synthesis, without precluding indirect mechanisms. These results indicate that molting hormone stimulates at least one universal route of its own inactivation by inducing ecdysteroid 26-hydroxylase activity and are discussed in relation to an analogous phenomenon observed for vitamin D

20 ANSWER 5 OF 23 SCISEARCH COPYRIGHT 1999 ISI (R)
TI QUANTITATIVE STRUCTURE-ACTIVITY STUDIES OF INSECT GROWTH-REGULATORS .10. SUBSTITUENT EFFECTS ON LARVICIDAL ACTIVITY OF 1-TERT-BUTYL-1-(2-CHLOROBENZOYL)-2-(SUBSTITUTED BENZOYL)**HYDRAZINES** AGAINST CHILO-SUPPRESSALIS AND DESIGN SYNTHESIS OF POTENT DERIVATIVES
SO PESTICIDE BIOCHEMISTRY AND PHYSIOLOGY, (FEB 1994) Vol. 48, No. 2, pp. 135-144.
ISSN: 0048-3575.
AU OIKAWA N; NAKAGAWA Y; NISHIMURA K (Reprint); UENO T; FUJITA T
AB The larvicidal activity of 1-tert-butyl-1-(2-chlorobenzoyl)-2-(substituted benzoyl)**hydrazines** was measured against the rice stem borer (Chilo suppressalis) in the presence of piperonyl butoxide, an inhibitor of oxidative metabolism. Variations in the activity were quantitatively examined by use of physicochemical substituent parameters and regression analysis. The results indicated that the hydrophobicity of substituents is favorable in general but the bulkiness of substituents is unfavorable position-specifically. The most favorable substitution pattern is the para substitution with lower alkyls and halogens. Compounds in which substitution patterns are simultaneously optimized in two benzene rings in the molecule were designed and prepared according to the present and previous quantitative analyses. Some of them, including 1-tert-butyl-1-(3,5-dichloro- and 3,5-dimethylbenzoyl)-2-(4-ethylbenzoyl) **hydrazines** the second being RH-5992, were about 20-30 times as larvicidal as the unsubstituted compound, RH-5849, against the rice stem borer. (C

L20 ANSWER 6 OF 23 MEDLINE
TI RH-5849, a **nonsteroidal ecdysone agonist**, does not mimic makisterone-A in Dysdercus koenigii.
SO EXPERIENTIA, (1994 May 15) 50 (5) 461-4.
Journal code: EQZ. ISSN: 0014-4754.
AU Koul O; Kapil R S
AB The response of final instar nymphs of Dysdercus koenigii to topical application of the non-steroidal **ecdysone agonist**, RH-5849, was dose dependent. The candidate compound produced mortality even at moderate doses, but precocious adult development was not observed. Similar results were obtained after oral administration or injection. Conversely, injections of makisterone-A (the principal moulting hormone of Dysdercus) into 5th instar nymphs resulted in precocious adult development within 4 days. We conclude that RH-5849 does not mimic makisterone-A, as is the case with **ecdysone**, and that toxicity is mediated instead

L8 ANSWER 2 OF 31 CAPLUS COPYRIGHT 1999 ACS
TI Other hormonal agents: **ecdysone agonists**
SO BCPC Monogr. (1989), 43(Prog. Prospects Insect Control), 107-18
CODEN: MBCCDO; ISSN: 0306-3941
AU Wing, K. D.; Ramsay, J. R.
AB A review with 34 refs. The novel insect growth regulator RH 5849 (1,2-dibenzoyl, 1-tert-Bu hydrazine), is the first **nonsteroidal ecdysone mimic** as detd. by data from Drosophila melanogaster and Plodia interpunctella tissue culture cells, **ecdysone** receptor exts. therefrom, and Manduca sexta larvae; this seems to be its primary mode of action in Lepidoptera. It also has chemosterilant activity on female Diptera, Coleoptera and Lepidoptera. RH 5849 thus represents a prototype ligand for a novel, invertebrate-specific target site.

L4 ANSWER 26 OF 53 SCISEARCH COPYRIGHT 1999 ISI (R)
TI ECDYSTEROID RECEPTOR-BINDING ACTIVITY AND ECDYSTEROID AGONIST ACTIVITY AT THE LEVEL OF GENE-EXPRESSION ARE CORRELATED WITH THE ACTIVITY OF DIBENZOYL **HYDRAZINES** IN LARVAE OF BOMBYX-MORI
SO JOURNAL OF INSECT PHYSIOLOGY, (OCT 1996) Vol. 42, No. 10, pp. 937-941. ISSN: 0022-1910.
AU MIKITANI K (Reprint)
AB Ecdysteroid activities of two dibenzoyl **hydrazines** (RH 5849 and RH 5992) were examined using the Kc cell line. Gene expression activity was determined in the transient assay utilizing the ecdysteroid responsive Drosophila melanogaster hsp27 promoter gene. Ecdysteroid receptor binding (EC(50) = 3.0 x 10(-7) M), induction of ecdysteroid responsive gene expression (EC,, = 3.0 x 10(-6) M) and induction of cell morphological change (EC(50) = 3.0 x 10(-7) M) were 13-fold, 7-fold and 13-fold higher in RH 5992 than in RH 5849, respectively. The addition of 10 ppm RH 5849 to the diet induced head capsule slippage in Bombyx mori larvae and most of the larvae died, RH 5992 caused the same response at 1 ppm. The higher insecticidal activity of RH 5992 compared to RH 5849 is likely caused by its higher ecdysteroid agonist activity at the molecular

L8 ANSWER 1 OF 31 MEDLINE
TI RH 5849, a **nonsteroidal ecdysone agonist**: effects on a Drosophila cell line.
SO SCIENCE, (1988 Jul 22) 241 (4864) 467-9.
Journal code: UJ7. ISSN: 0036-8075.
AU Wing K D
AB The steroid molting hormone 20-hydroxyecdysone is the physiological inducer of molting and metamorphosis in insects. In **ecdysone** -sensitive Drosophila Kc cells, the insecticide RH 5849 (1,2-dibenzoyl-1-tert-butylhydrazine) **mimics** the action of 20-hydroxyecdysone by causing the formation of processes, an inhibition of cell proliferation, and induction of acetylcholinesterase. RH 5849 also competes with [3H]ponasterone A for high-affinity **ecdysone** receptor sites from Kc cell extracts. Resistant cell populations selected by growth in the continued presence of either RH 5849 or 20-hydroxyecdysone are insensitive to both compounds and exhibit a decreased titer of measurable **ecdysone** receptors. Although it is less potent than 20-hydroxyecdysone in both whole-cell and cell-free receptor assays, RH 5849 is the first **nonsteroidal**

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Proc Natl Acad Sci U S A 2001 Mar 27;98(7):3867-72

The dual role of ultraspiracle, the Drosophila retinoid X receptor, in the ecdysone response.

Ghbeish N, Tsai CC, Schubiger M, Zhou JY, Evans RM, McKeown M

Department of Biology, University of California at San Diego, La Jolla, CA 92093, USA.

The Drosophila homolog of the retinoid X receptor, ultraspiracle (USP), heterodimerizes with the ecdysone receptor (EcR) to form a functional complex that mediates the effects of the steroid molting hormone ecdysone by activating and repressing expression of ecdysone response genes. As with other retinoid X receptor heterodimers, EcR/USP affects gene transcription in a ligand-modulated manner. We used in vivo, cell culture, and biochemical approaches to analyze the functions of two usp alleles, usp(3) and usp(4), which encode stable proteins with defective DNA-binding domains. We observed that USP is able to activate as well as repress the Z1 isoform of the ecdysone-responsive broad complex (BrC-Z1). Activation of BrC-Z1 as well as EcR, itself an ecdysone response gene, can be mediated by both the USP3 and USP4 mutant proteins. USP3 and USP4 also activate an ecdysone-responsive element, hsp27EcRE, in cultured cells. These results differ from the protein null allele, usp(2), which is unable to mediate activation [Schubiger, M. & Truman, J. W. (2000) Development 127, 1151--1159]. BrC-Z1 repression is compromised in all three usp alleles, suggesting that repression involves the association of USP with DNA. Our results distinguish two mechanisms by which USP modulates the properties of EcR: one that involves the USP DNA-binding domain and one that can be achieved solely through the ligand-binding domain. These newly revealed properties of USP might implicate similar properties for retinoid X receptor.

PMID: 11274407, UI: 21173650

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Proc Natl Acad Sci U S A 2001 Feb 13;98(4):1549-54

The structure of the ultraspiracle ligand-binding domain reveals a nuclear receptor locked in an inactive conformation.

Clayton GM, Peak-Chew SY, Evans RM, Schwabe JW

Medical Research Council, Laboratory of Molecular Biology, Cambridge CB2 2QH, United Kingdom.

Ultraspiracle (USP) is the invertebrate homologue of the mammalian retinoid X receptor (RXR). RXR plays a uniquely important role in differentiation, development, and homeostasis through its ability to serve as a heterodimeric partner to many other nuclear receptors. RXR is able to influence the activity of its partner receptors through the action of the ligand 9-cis retinoic acid. In contrast to RXR, USP has no known high-affinity ligand and is thought to be a silent component in the heterodimeric complex with partner receptors such as the ecdysone

receptor. Here we report the 2.4-A crystal structure of the USP ligand-binding domain. The structure shows that a conserved sequence motif found in dipteran and lepidopteran USPs, but not in mammalian RXRs, serves to lock USP in an inactive conformation. It also shows that USP has a large hydrophobic cavity, implying that there is almost certainly a natural ligand for USP. This cavity is larger than that seen previously for most other nuclear receptors. Intriguingly, this cavity has partial occupancy by a bound lipid, which is likely to resemble the natural ligand for USP.

PMID: 11171988, UI: 21117075

Proc Natl Acad Sci U S A 2000 Dec 19;97(26):14512-7

Identification of ligands and coligands for the ecdysone-regulated gene switch.

Saez E, Nelson MC, Eshelman B, Banayo E, Koder A, Cho GJ, Evans RM

The Salk Institute for Biological Studies, Howard Hughes Medical Institute, 10010 North Torrey Pines Road, La Jolla, CA 92037, USA.

The ecdysone-inducible gene switch is a useful tool for modulating gene expression in mammalian cells and transgenic animals. We have identified inducers derived from plants as well as certain classes of insecticides that increase the versatility of this gene regulation system. Phytoecdysteroids share the favorable kinetics of steroids, but are inert in mammals. The gene regulation properties of one of these ecdysteroids have been examined in cell culture and in newly developed strains of ecdysone-system transgenic mice. Ponasterone A is a potent regulator of gene expression in cells and transgenic animals, enabling reporter genes to be turned on and off rapidly. A number of nonsteroidal insecticides have been identified that also activate the ecdysone system. Because the gene-controlling properties of the ecdysone switch are based on a heterodimer composed of a modified ecdysone receptor (VgEcR) and the retinoid X receptor (RXR), we have tested the effect of RXR ligands on the VgEcR/RXR complex. Used alone, RXR ligands display no activity on the ecdysone switch. However, when used in combination with a VgEcR ligand, RXR ligands dramatically enhance the absolute levels of induction. This property of the heterodimer has allowed the development of superinducer combinations that increase the dynamic range of the system.

PMID: 11114195, UI: 20570511

Mol Cell 1999 Aug;4(2):175-86

SMRTER, a Drosophila nuclear receptor coregulator, reveals that EcR-mediated repression is critical for development.

Tsai CC, Kao HY, Yao TP, McKeown M, Evans RM

Gene Expression Lab, Salk Institute, La Jolla, California 92037, USA.

The Drosophila ecdysone receptor (EcR)/ultraspiracle (USP) heterodimer is a key regulator in molting and metamorphoric processes, activating and repressing transcription in a sequence-specific manner. Here, we report the isolation of an EcR-interacting protein, SMRTER, which is structurally divergent but functionally similar to the vertebrate nuclear corepressors SMRT and N-CoR. SMRTER mediates repression by interacting with Sin3A, a repressor known to form a complex with the histone deacetylase Rpd3/HDAC. Importantly, we identify an EcR mutant allele that fails to bind SMRTER and is characterized by developmental defects and lethality. Together, these results reveal a novel nuclear receptor cofactor that exhibits evolutionary conservation in the mechanism to achieve repression and demonstrate the essential role of repression in hormone signaling.

PMID: 10488333, UI: 99417957

Proc Natl Acad Sci U S A 1997 Mar 18;94(6):2278-83

Coexpression of nuclear receptor partners increases their solubility and biological activities.

Li C, Schwabe JW, Banayo E, Evans RM

The Salk Institute for Biological Studies, Gene Expression Laboratory, La Jolla, CA 92037, USA.

The biological activities of the retinoids are mediated by two nuclear hormone receptors: the retinoic acid receptor (RAR) and the retinoid-X receptor (RXR). RXR (and its insect homologue ultraspiracle) is a common heterodimeric partner for many other nuclear receptors, including the insect ecdysone receptor. As part of a continuing analysis of nuclear receptor function, we noticed that, whereas RXR can be readily expressed in Escherichia coli to produce soluble protein, many of its heterodimeric partners cannot. For example, overexpression of RAR results mostly in inclusion bodies with the residual soluble component unable to interact with RXR or ligand efficiently. Similar results are seen with other RXR/ultraspiracle partners. To overcome these problems, we designed a novel double cistronic vector to coexpress RXR and its partner ligand-binding domains in the same bacterial cell. This resulted in a dramatic increase in production of soluble and apparently stable heterodimer. Hormone-binding studies using the purified RXR-RAR heterodimer reveal increased ligand-binding capacity of both components of 5- to 10-fold, resulting in virtually complete functionality. Based on these studies we find that bacterially expressed receptors can exist in one of three distinct states: insoluble, soluble but unable to bind ligand, or soluble with full ligand-binding capacity. These results suggest that coexpression may represent a general strategy for biophysical and structural analysis of receptor complexes.

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Proc Natl Acad Sci U S A 1996 Apr 16;93(8):3346-51

Ecdysone-inducible gene expression in mammalian cells and transgenic mice.

No D, Yao TP, Evans RM

Howard Hughes Medical Institute, Salk Institute for Biomedical Studies, La Jolla, CA 92037, USA.

During metamorphosis of Drosophila melanogaster, a cascade of morphological changes is triggered by the steroid hormone 20-OH ecdysone via the ecdysone receptor, a member of the nuclear receptor superfamily. In this report, we have transferred insect hormone responsiveness to mammalian cells by the stable expression of a modified ecdysone receptor that regulates an optimized ecdysone responsive promoter. Inductions reaching 4 orders of magnitude have been achieved upon treatment with hormone. Transgenic mice expressing the modified ecdysone receptor can activate an integrated ecdysone responsive promoter upon administration of hormone. A comparison of tetracycline-based and ecdysone-based inducible systems reveals the ecdysone regulatory system exhibits lower basal activity and higher inducibility. Since ecdysone administration has no apparent effect on mammals, its use for regulating genes should be excellent for transient inducible expression of any gene in transgenic mice and for gene therapy.

PMID: 8622939, UI: 96194971

Mol Cell Biol 1995 Dec;15(12):6736-45

Seven-up inhibits ultraspiracle-based signaling pathways in vitro and in vivo.

Zelhof AC, Yao TP, Chen JD, Evans RM, McKeown M

Department of Biology, University of California, San Diego, La Jolla 92093, USA.

Seven-up (Svp), the Drosophila homolog of the chicken ovalbumin upstream transcription factor (COUP-TF); Ultraspiracle (Usp), the Drosophila homolog of the retinoid X receptor; and the ecdysone receptor are all members of the nuclear/steroid receptor superfamily. COUP-TF negatively regulates hormonal signaling involving retinoid X receptor in tissue culture systems. Here we demonstrate that Svp, like COUP-TF, can modulate Ultraspiracle-based hormonal signaling both in vitro and in vivo. Transfection assays in CV-1 cells demonstrate that Seven-up can inhibit ecdysone-dependent transactivation by the ecdysone receptor complex, a heterodimeric complex of Usp and ecdysone receptor. This repression depends on the dose of Svp and occurs with two different Drosophila ecdysone response elements. Ectopic expression of Svp in vivo induces lethality during early metamorphosis, the time of maximal ecdysone responsiveness. Concomitant overexpression of Usp rescues the larvae from the lethal effects of Svp. DNA binding studies show that Svp can bind to various direct repeats of the sequence AGGTCA but cannot bind to one of the ecdysone response elements used in the transient transfection assays. Our results suggest that Svp-mediated repression can occur by both DNA binding competition and protein-protein interactions.

PMID: 8524239, UI: 96069382

Proc Natl Acad Sci U S A 1995 Nov 7;92(23):10477-81

Identification and characterization of a Drosophila nuclear receptor with the ability to inhibit the ecdysone response.

Zelhof AC, Yao TP, Evans RM, McKeown M

Department of Biology, University of California, San Diego, La Jolla 92093, USA.

In a search for retinoid X receptor-like molecules in Drosophila, we have identified an additional member of the nuclear receptor superfamily, XR78E/F. In the DNA-binding domain, XR78E/F is closely related to the mammalian receptor TR2, as well as to the nuclear receptors Coup-TF and Seven-up. We demonstrate that XR78E/F binds as a homodimer to direct repeats of the sequence AGGTCA. In transient transfection assays, XR78E/F represses ecdysone signaling in a DNA-binding-dependent fashion. XR78E/F has its highest expression in third-instar larvae and prepupae. These experiments suggest that XR78E/F may play a regulatory role in the transcriptional cascade triggered by the hormone ecdysone in Drosophila.

PMID: 7479823, UI: 96068638

Nature 1993 Dec 2;366(6454):476-9

Functional ecdysone receptor is the product of EcR and Ultraspiracle genes.

Yao TP, Forman BM, Jiang Z, Cherbas L, Chen JD, McKeown M, Cherbas P, Evans RM

Howard Hughes Medical Institute, Salk Institute for Biological Studies, La Jolla, California 92037.

Although the biological activity of the insect moulting hormone ecdysone, is manifested through a hormonally regulated transcriptional cascade associated with chromosomal puffing, a direct association of the receptor with the puff has yet to be established. The cloned ecdysone receptor (EcR) is by itself incapable of high-affinity DNA binding or transcriptional activation. Rather, these activities are dependent on heterodimer formation with Ultraspiracle (USP) the insect homologue of vertebrate retinoid X receptor. Here we report that native EcR and USP are co-localized on ecdysone-responsive loci of polytene chromosomes. Moreover, we show that natural ecdysones selectively promote physical association between EcR and USP, and conversely, that high-affinity hormone binding requires both EcR and USP. Replacement of USP with retinoid X receptor produces heterodimers with distinct pharmacological and functional properties. These results redefine the ecdysone receptor as a dynamic complex whose activity may be altered by combinatorial interactions among subunits and ligand.

PMID: 8247157, UI: 94067348

Cell 1992 Oct 2;71(1):63-72

Drosophila ultraspiracle modulates ecdysone receptor function via heterodimer formation.

Yao TP, Segraves WA, Oro AE, McKeown M, Evans RM

Howard Hughes Medical Institute, La Jolla, California.

The vertebrate retinoid X receptor (RXR) has been implicated in the regulation of multiple hormonal signaling pathways through the formation of heteromeric receptor complexes that bind DNA with high affinity. We now demonstrate that ultraspiracle (usp), a Drosophila RXR homolog, can substitute for RXR in stimulating the DNA binding of receptors for retinoic acid, T3, vitamin D, and peroxisome proliferator activators. These observations led to the search and ultimate identification of the ecdysone receptor (EcR) as a Drosophila partner of usp. Together, usp and EcR bind DNA in a highly cooperative fashion. Cotransfection of both EcR and usp expression vectors is required to render cultured mammalian cells ecdysone responsive. These results implicate usp as an integral component of the functional EcR. By demonstrating that receptor heterodimer formation precedes the divergence of vertebrate and invertebrate lineages, these data underscore a central role for RXR and its homolog usp in the evolution and control of the nuclear receptor-based endocrine system.

PMID: 1327536, UI: 93008244

Curr Opin Genet Dev 1992 Apr;2(2):269-74

The Drosophila nuclear receptors: new insight into the actions of nuclear receptors in development.

Oro AE, McKeown M, Evans RM

Howard Hughes Medical Institute, Gene Expression Lab, La Jolla, California 92186-5800.

In Drosophila melanogaster, an increasing number of members of the steroid hormone receptor superfamily are being identified and characterized. Molecular and genetic analysis of receptor function provides evidence for a set of functions underlying the determination of pattern formation, metamorphosis, eye development, and reproduction. Many of the Drosophila receptor genes show striking homologies to mammalian receptor genes. This suggests that genetic analysis in flies could facilitate the generation of biological models that pertain to complex hormonal responses in development and which are relevant to both vertebrate and invertebrate systems.

Publication Types:

- Review
- Review, academic

PMID: 1638122, UI: 92345839

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Proc Natl Acad Sci U S A 1996 Apr 16;93(8):3346-51

Ecdysone-inducible gene expression in mammalian cells and transgenic mice.

No D, Yao TP, Evans RM

Howard Hughes Medical Institute, Salk Institute for Biomedical Studies, La Jolla, CA 92037, USA.

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PMID: 8622939, UI: 96194971

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Proc Natl Acad Sci U S A 1988 Apr;85(7):2096-100

26-[125I]iodoponasterone A is a potent ecdysone and a sensitive radioligand for ecdysone receptors.

Cherbas P, Cherbas L, Lee SS, Nakanishi K

Department of Biology, Indiana University, Bloomington 47405.

The effects of ecdysone, the steroid molting hormone of arthropods, are of considerable interest both to insect physiologists and to those studying steroid-regulated gene expression. Yet progress in understanding ecdysone receptors has been inhibited by the lack of a suitable highly radioactive hormone analog with high affinity for the receptor. Here we report that the synthetic ecdysteroid 26-iodoponasterone A is one of the most active ecdysones known, inducing half-maximal morphological transformation in Drosophila Kc167 cells when present at 0.5 nM. 26-[125I]Iodoponasterone A can be prepared at a specific activity of 2175 Ci/mmol (1 Ci = 37 GBq) by reaction of the precursor 26-mesylinokosterone with carrier-free Na125I. The radiolabeled material binds to Kc167 cell ecdysone receptors specifically and with affinity (Kd ca. 3.8 X 10(-10) M). Thus, 26-[125I]iodoponasterone A appears to be a superior radioligand for ecdysone receptors on grounds both of affinity and of specific activity. Its

ready availability should greatly facilitate studies of these receptors.

PMID: 3127825, UI: 88176893

Cell 1993 Jul 2;73(7):1323-37

Drosophila tissues with different metamorphic responses to ecdysone express different ecdysone receptor isoforms.

Talbot WS, Swyryd EA, Hogness DS

Department of Biochemistry, Stanford University School of Medicine, California 94305.

In D. melanogaster a pulse of the steroid hormone ecdysone triggers the larval-to-adult metamorphosis, a complex process in which this hormone induces imaginal tissues to generate adult structures and larval tissues to degenerate. We show that the EcR gene encodes three ecdysone receptor isoforms (EcR-A, EcR-B1, and EcR-B2) that have common DNA- and hormone-binding domains but different N-terminal regions. We have used isoform-specific monoclonal antibodies to show that at the onset of metamorphosis different ecdysone target tissues express different isoform combinations in a manner consistent with the proposition that the different metamorphic responses of these tissues require different combinations of the EcR isoforms. We have also determined temporal developmental profiles of the EcR isoforms and their mRNAs in whole animals, showing that different isoforms predominate at different developmental stages that are marked by a pulse of ecdysone.

PMID: 8324824, UI: 93313962

Mol Cell Biol 1993 Nov;13(11):7101-11

Isolation and characterization of fifteen ecdysone-inducible Drosophila genes reveal unexpected complexities in ecdysone regulation.

Hurban P, Thummel CS

Department of Human Genetics, Howard Hughes Medical Institute, University of Utah, Salt Lake City 84112.

Our insights into the regulatory mechanisms by which the steroid hormone ecdysone triggers Drosophila melanogaster metamorphosis have largely depended on puffs in the larval salivary gland polytene chromosomes as a means of identifying genes of interest. Here, we describe an approach that provides access to ecdysone-inducible genes that are expressed in most larval and imaginal tissues, regardless of their ability to form puffs in the polytene chromosomes. Several hundred cDNAs were picked at random from subtracted cDNA libraries and subjected to a rapid and sensitive screen for their ability to detect mRNAs induced by ecdysone in the presence of cycloheximide. Of the 15 genes identified in this manner, 2 correspond to early puffs in the salivary gland polytene chromosomes, at 63F and 75B, confirming that this screen functions at the desired level of sensitivity and is capable of identifying novel primary-response genes. Three of the genes, Eig45-1, Eig58, and Eig87, are expressed coordinately with the salivary gland early genes; one of them, Eig58, maps to the 58BC puff that is active

when the 74EF and 75B early puffs are at their maximal size. Another gene identified in this screen, Eig17-1, encodes a novel cytochrome P-450. On the basis of its sequence identity and temporal profile of expression, this gene may play a role in steroid hormone metabolism and thus could provide a mechanism for feedback regulation of ecdysone production. Although all 15 genes have patterns of transcription that are consistent with ecdysone regulation in vivo, 5 genes do not appear to be induced by the late larval ecdysone pulse. This indicates that ecdysone induction in larval organs cultured with cycloheximide is not always indicative of a primary response to the hormone.

PMID: 8413299, UI: 94019381

Nucleic Acids Res 1989 Sep 25;17(18):7167-78

A member of the steroid hormone receptor gene family is expressed in the 20-OH-ecdysone inducible puff 75B in Drosophila melanogaster.

Feigl G, Gram M, Pongs O

Lehrstuhl fur Biochemie, Ruhr-Universitat Bochum, FRG.

Drosophila melanogaster DNA has been cloned which encompasses a major part of the 20-OH-ecdysone inducible puff 75B. One 20-OH-ecdysone responsive transcription unit was detected which is expressed into two transcripts which accumulate upon the incubation of salivary glands of 3rd instar larvae with 20-OH-ecdysone. This accumulation is correlated with the 20-OH-ecdysone induced activity of puff 75B. 75B cDNA analysis indicates that the activity of puff 75B leads to the synthesis of a protein which belongs to the steroid and thyroid hormone receptor superfamily. The highest similarity of the derived 75B protein sequence was found to the DNA and ligand binding domains of human retinoic acid receptor. A study of the tissue distribution in larvae revealed that 75B mRNA is present in most, if not all 20-OH-ecdysone target tissues. It is proposed that 75B protein is a DNA-binding protein playing a key role in mediating the regulation of the larval molt by 20-OH-ecdysone.

PMID: 2508058, UI: 90016778

Nature 1993 Apr 1;362(6419):471-5

Heterodimerization of the Drosophila ecdysone receptor with retinoid X receptor and ultraspiracle.

Thomas HE, Stunnenberg HG, Stewart AF

Gene Expression Programme, EMBL, Heidelberg, Germany.

Ecdysone in Drosophila has been a paradigm for steroid hormones since its ability to induce gene activity directly was demonstrated by its effects on moulting and polytene chromosome puffing. The ecdysone receptor (EcR) was recently confirmed as a member of the nuclear receptor superfamily by cloning and characterization in a Drosophila cell line. Here we show that EcR needs to heterodimerize with either the retinoid X receptor (RXR) or its Drosophila

homologue, ultraspiracle (USP), for DNA binding and transactivation. These results place the ecdysone receptor in the heterodimerizing class of the nuclear receptor superfamily and demonstrate that the role of RXR/USP as a central and promiscuous partner in mediating the activity of these receptors is highly conserved. Whereas EcR-USP DNA-binding activity is unaffected by hormone, EcR-RXR DNA-binding activity is stimulated by either ecdysteroid or 9-cis-retinoic acid, demonstrating that hormone can play a role in heterodimer stabilization.

PMID: 8385270, UI: 93218726

Curr Opin Biotechnol 1997 Oct;8(5):608-16

Inducible gene expression in mammalian cells and transgenic mice.

Saez E, No D, West A, Evans RM

Howard Hughes Medical Institute, Gene Expression Lab, Salk Institute, La Jolla, CA 92037, USA. esaez@aim.salk.edu

Advances in biomedicine have accentuated the need to develop methods to deliberately modulate gene activity. In addition to improved versions of the system based on components of the tetracycline resistance operon, several strategies have recently emerged to control gene function at the transcriptional level. Particularly promising are approaches based on non-mammalian steroid hormones, and on small molecules that bind immunophilins.

Publication Types:

- Review
- Review, tutorial

PMID: 9353233, UI: 98028782

Nature 1993 Dec 2;366(6454):476-9

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selectively promote physical association between EcR and USP, and conversely, that high-affinity hormone binding requires both EcR and USP. Replacement of USP with retinoid X receptor produces heterodimers with distinct pharmacological and functional properties. These results redefine the ecdysone receptor as a dynamic complex whose activity may be altered by combinatorial interactions among subunits and ligand.

PMID: 8247157, UI: 94067348

Trends Genet 1996 Aug;12(8):306-10

Files on steroids--Drosophila metamorphosis and the mechanisms of steroid hormone action.

Thummel CS

Howard Hughes Medical Institute, University of Utah, Salt Lake City 84112, USA. carl.thummel@genetics.utah.edu

Recent studies have provided new insights into the molecular mechanisms by which the steroid hormone ecdysone triggers the larval-to-adult metamorphosis of Drosophila. Ecdysone-induced transcription factors activate large sets of secondary-response genes and provide the competence for subsequent regulatory responses to the hormone. It seems likely that similar hormone-triggered regulatory hierarchies exist in other higher organisms and that Drosophila is providing our first glimpses of the complexities of these gene networks.

Publication Types:

- Review
- Review, tutorial

PMID: 8783940, UI: 96378362